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SUSPENSIONS OF MICRON-SIZED ASCORBIC ACID PARTICLES AND THEIR USE AS ANTIOXIDANTS

FIELD OF THE INVENTION

Ascorbic acid and its use as an antioxidant for the stabilization of lipids, carotenoids, and the like against oxidation and color fading.

According to the present invention, oxidation of lipids and degradation of carotenoids is inhibited by solid particles of ascorbic acid which are below 38 microns in size, especially when suspended in an oleogenous substrate in which they are insoluble, or in a mixture with carotenoids and the like. The preparation and use of such solid ascorbic acid particles and of suspensions of such solid ascorbic acid particles is disclosed.

BACKGROUND OF THE INVENTION AND PRIOR ART

Oxidation of fats, vegetable oils, carotenoids and their biologically active derivatives, Vitamin A, and of essential oils and other flavorings results in degradation of their quality, and is deleterious to foodstuffs containing the oxidized products.

The art shows many methods of inhibiting lipid oxidation by adding fat-soluble antioxidants to the substrate. The art does not show the stabilization of fats

by the use of undissolved ascorbic acid particles of any size. The lipid-soluble antioxidants include synthetics, such as BHA and BHT, or natural antioxidants, such as Labiatae extracts, and particularly rosemary and sage extracts. Fat-soluble esters of ascorbic acid are also used. The synthetic antioxidants are normally dissolved in the fat at levels not to exceed their permitted limits of 0.02%, whereas the natural antioxidants may be used at higher levels if their flavor level is not objectionable in the particular food or fat. Tocopherols, being naturally present in vegetable oils, may be added to animal fats to increase stability. In vegetable oils, they act as pro-oxidants at levels above about 2000 ppm.

Ascorbic acid, which is water soluble and fat insoluble, is a common additive to foods, where it serves to increase the Vitamin C content. In citrus beverages, it has been claimed to improve the flavor, and in pickle brines to improve the freshness. An important use is in curing brines in combination with nitrates and nitrites. In the curing of the meat, it reacts to form nitrous oxides, which in turn react with heme pigments to form the stable red colors of cured meats. It has been suggested that it reduces the formation of nitrosamines during the cooking of such meats.

Ascorbic acid has been used as an antioxidant from time immemorial. However, a search in U.S. Patent Office classes and subclasses, namely, Class 426, Subclasses 96, 98, 250, 534, 536, 540, 541, 547, 638, and 654; Class 260, Subclass 398.5; Class 252, Subclasses 314 and 363.5; Class 585, Subclass 351; and Class 514, Subclass 772, revealed no suggestion of the present invention. An update of the search in the U.S. Patent Office Class 426, Subclasses 72, 541, 544, 545, 546, 653, and 654; Class 424, Subclass 441;

and Class 106, Subclass 263, and I.P.C. B 29C 49/00, extending over approximately the past year, and references cited in related applications, revealed only the following developments:

Ascorbic acid has been dissolved in an aqueous algae solution prior to spray drying, where it may reduce degradation due to the stresses of that operation.

It has been dissolved in aqueous solutions of tea extract, to extend the antioxidant power of the tea.

It is used as an acidulant, either in beverages per se, or incorporated into a gum matrix including polyvinyl acetate which releases it slowly upon chewing of the gum.

It is less preferred than glucose-glucose oxidase/catalase as an oxygen scavenger in aqueous phases of emulsions, and it is used in aqueous solutions of cosmetics.

Solid ascorbic acid is used in vitamin tablets. In some applications, it may be coated with a fatty acid, to permit adhesion of the particles to the surface of a dried food. It may be a component in a fat plug in baker's margarine, wherein the plug is designed to keep the components included in it from undesirably affecting the flavor of the margarine, but assisting the baker when incorporated in a dough.

Encapsulation of carotenoids in gelatin is an accepted method of reducing the rate at which they degrade. Similar retardation of oxidation is achieved by encapsulating fats or other substances in capsules, or coating the particles with an oxygen and light barrier such as an opaque sugar layer.

It has been dissolved in ethanol, which in turn is added to a mixture of lecithin and tocopherols, to form a transparent liquid upon removal of the ethanol. This

ternary composition of ascorbic acid is suggested for use in highly unsaturated fats, in which it exhibits greater effectiveness than mixtures of tocopherol and lecithin alone.

In a pending application, I have disclosed ascorbic acid dissolved in a volatile solvent, such as methanol and water, and thence transferred into solution in a non-ionic emulsifier, with the solvent subsequently being removed. This forms an "activated ascorbic acid," which has powerful antioxidant properties in oleogenous media or with carotenoids and the like. Other of my pending applications show synergistic mixtures of natural antioxidants and certain emulsifiers as stabilizers for carotenoids.

Solid ascorbic acid has not been used or suggested for use as an antioxidant or stabilizer for fats or carotenoids, so far as can be ascertained, because it is insoluble in lipid media.

OBJECTS OF THE INVENTION

It is an object of the present invention to provide a new solid particulate form of ascorbic acid, having a particle size less than about 38 microns on its largest dimension, the crystals thereof having irregular shapes, which is characterized by improved antioxidant and anti-fading properties in lipids, oils, carotenoids, and like fatty foods, flavors, and colors. Another object is the provision of such particles in an oleogenous medium in which they are insoluble. A further object is the provision of such compositions which also comprise a natural oil-soluble antioxidant, especially of the Labiatae genus. A further object is the provision of such compositions comprising also a non-ionic surface-active agent, which still further increases the antioxidant activity of such

compositions. A still further object is the employment of such compositions in the stabilization of fats, fatty foods, and the like against oxidation and color fading, and another object is the provision of a fat or fatty food or other material so stabilized by the employment of a suitable stabilizing or antioxidant amount of either the novel solid ascorbic acid particles per se or in an oleogenous medium in which they are insoluble, optionally together with a natural antioxidant and/or a non-ionic surface-active agent or emulsifier, the fat or fatty material in any event being thus protected against oxidative degradation and color fading. Yet other objects will become apparent hereinafter and yet additional objects will be apparent to one skilled in the art.

SUMMARY OF THE INVENTION

My invention then comprises, inter alia, the following, singly or in combination:

An antioxidant composition consisting essentially of solid particles of ascorbic acid which are less than about 38 microns in size on their largest dimension; such a

composition wherein at least about 50% of the solid particles of ascorbic acid are less than about 10 microns in size on their largest dimension; such a

composition wherein essentially all of the particles are about 20 microns or less on their largest dimension; and such a

composition comprising also a natural oil-soluble antioxidant. Moreover, a

fat or oil composition, optionally containing a carotenoid, which is protected from oxidative degradation by a suspension of 0.001% or more by weight of ascorbic acid particles which are less than about 38 microns in size on their largest dimension; such a

composition wherein at least about 50% of the solid particles of ascorbic acid are less than about 10 microns in size on their largest dimension; such a

composition wherein at least about 50% of the solid particles of ascorbic acid are less than about 5 microns in size on their largest dimension and essentially all of the particles are about 20 microns or less on their largest dimension; and such a

composition, optionally containing a carotenoid, which is protected from oxidative degradation by a suspension of .002% or more by weight of such ascorbic acid particles, and which optionally contains a natural oil-soluble antioxidant. Further, an

antioxidant composition consisting essentially of a suspension of solid ascorbic acid particles in a medium, preferably in an edible oleogenous medium, in which they are insoluble, the solid particles of ascorbic acid being less than about 38 microns in size on their largest dimension; such an

antioxidant composition wherein at least about 50% of the solid particles of ascorbic acid are less than about 10 microns in size on their largest dimension; such an

antioxidant composition wherein at least about 50% of the solid particles of ascorbic acid are less than about 5 microns in size on their largest dimension; such an

antioxidant composition wherein essentially all of the particles are about 20 microns or less on their largest dimension; such an

antioxidant composition comprising also a natural oil-soluble antioxidant; such an

antioxidant composition wherein the concentration of ascorbic acid particles of less than about 38 micron size in the medium is between about 5% and 50% by weight; and such an

antioxidant composition wherein the ascorbic acid particles of less than about 38 micron size have irregular shapes and their concentration in the medium is between about 20% and 35% by weight. In addition, a

fat or oil composition, optionally containing a carotenoid, which is protected from oxidative degradation by a suspension of 0.001% or more by weight of an antioxidant composition consisting essentially of a suspension of solid ascorbic acid particles, having a size less than about 38 microns on their largest dimension, in a medium, preferably an edible oleogenous medium, in which they are insoluble; such a

composition wherein at least about 50% of the solid particles of ascorbic acid are less than about 10 microns in size on their largest dimension; such a

composition wherein at least about 50% of the solid particles of ascorbic acid are less than about 5 microns in size on their largest dimension; such a

composition wherein the antioxidant composition consists essentially of solid particles of ascorbic acid of about 20 microns or less in size on their largest dimension; such a

composition wherein the composition comprises also a natural oil-soluble antioxidant; such a

composition wherein the concentration of ascorbic acid particles of less than about 38 micron size in the medium is between about 5% and 50% by weight; and such a

composition wherein the concentration of ascorbic acid in the medium is between about 10% and 35% by weight. Also, a

method of protecting an edible or other fat, oil, carotenoid, fatty food, or other substrate which is lipid in nature or which comprises a lipid phase, comprising the step of admixing the said substrate with an oxidation-protective amount of any of the foregoing antioxidant compositions; such a

method of protecting an edible fat, oil, and/or carotenoid by the addition thereto of at least about 0.002% by weight of solid ascorbic acid particles which are less than about 38 microns in size on their largest dimension; such a

method wherein the protected substrate comprises a member selected from the group consisting of: soy oil; canola oil; peanut oil; sunflower oil; chicken fat; pork fat; turkey fat; beef fat; a marine oil; a paprika carotenoid; an annatto carotenoid; canthaxanthin; astaxanthin; and beta-carotene; such a

method wherein the amount of the composition employed is calculated to provide an amount of microcrystalline ascorbic acid in the substrate of at least about 0.002% by weight; and such a

method wherein a natural antioxidant taken from the class consisting of Labiatae extracts, tea extracts, and tocopherol is also added to the substrate or is present in the antioxidant composition employed. Also, a

food or feed which is lipid in nature or which comprises a lipid phase in which the lipid or lipid phase is stabilized with an oxidation-protective amount of any of the foregoing antioxidant compositions; such a

food or feed wherein the amount of the composition employed is calculated to provide an amount of microcrystalline ascorbic acid in the food or feed of above about 0.001% by weight; such a

food or feed wherein the food or feed is protected with at least about 0.002% by weight of such solid ascorbic acid particles; such a

food or feed wherein the food or fat comprises a member selected from the group consisting of: soy oil; canola oil; peanut oil; sunflower oil; chicken fat; pork fat; turkey fat; beef fat; a marine oil; a paprika carotenoid; an annatto carotenoid; canthaxanthin; astaxanthin; and beta-carotene; such a

food or feed wherein the protective composition also comprises a natural oil-soluble antioxidant taken from the class consisting of Labiatae extracts, tea extracts, and tocopherol; and such a

food or feed wherein the amount of protective microcrystalline ascorbic acid in the substrate is at least about 0.005% by weight. Additionally, a

method of stabilizing the fatty phase of a cosmetic or an essential oil by admixing the fat with an oxidation-protective amount of an antioxidant composition consisting essentially of ascorbic acid particles which are less than about 38 microns in size on their longest dimension, optionally when suspended in a medium in which they are insoluble. Further, a

method of stabilizing Vitamin A by admixing the Vitamin A with an oxidation-protective amount of an antioxidant composition consisting essentially of ascorbic acid particles which are less than about 38 microns in size on their longest dimension, optionally when suspended in an

edible oleogenous medium in which they are insoluble. Finally such

antioxidant particles suspended in a nonionic surface-active agent; and such

antioxidant compositions including a nonionic surface-active agent; and a

stabilized fat or oil composition wherein the stabilizing composition comprises a nonionic surface-active agent; and a

stabilized fatty product wherein the stabilizing composition comprises an orally-ingestible nonionic surface-active agent; and such a

stabilization method wherein the stabilizing composition comprises a nonionic surface-active agent; and such an

antioxidant composition, stabilized product, and method wherein the surface-active agent is selected from the group consisting of

a. mono and di glycerides of fatty acids,

b. polyglyceride esters of fatty acids,

c. mono and diglyceride esters further esterified with a dibasic organic acid taken from the class consisting of citric, lactic, and tartaric acids,

d. acetylated mono and diglyceride esters further esterified with a dibasic organic acid taken from the class consisting of citric, lactic, and tartaric acids,

e. sorbitan esters of fatty acids,

f. propylene glycol esters of fatty acids, and

g. lecithin; and, finally, such an

antioxidant composition, stabilized product, and method wherein the surface-active agent comprises glycerol

mono-oleate, sorbitan mono-oleate, sorbitan trioleate, sorbitan monostearate, octaglycerol mono-oleate, or deca-glycerol capric caprylate.

GENERAL DESCRIPTION OF THE INVENTION

This invention discloses for the first time that a solid, undissolved particle of ascorbic acid, less than 38 microns in size, is an exceptionally powerful antioxidant for media in which the particles are insoluble. Unlike all of the prior art, it does not depend upon dissolution in a solvent such as water or alcohol to achieve its effectiveness. Indeed, one of the advantages of this invention is the avoidance of any solvent in the preparation of the antioxidant composition. Of critical importance is that the micron size of the particles be below about 38 microns on their largest dimension, and preferably below about 10 microns, and optimally the greatest part being below about 5 microns. Advantageously, all particles are below about twenty (20) microns on their greatest dimension. Ascorbic acid is a solid, which is readily soluble in water. To make it effective as a lipid antioxidant it must be reduced in size to below about 38 microns on its greatest dimension, as shown in the Examples, and the surface of the particles preferably wetted with an oleogenous material so that they will most advantageously act as an antioxidant. The reduction and wetting are advantageously performed by wet milling, such as in a paint mill or pebble mill. Less preferred is dry milling of granular ascorbic acid, since the <38 micron-sized particles must then be completely deaerated when mixed with the oil to be stabilized, to make them effective. Air may be occluded on their surfaces unless this precaution is taken.

Although, in aqueous systems, ascorbic acid has been reported to have pro-oxidant effects at high concentrations, in the lipid systems investigated this has not been the case. Accordingly, overdosing is not a risk. Since Vitamin C is an essential nutrient for both man and animals, and since in the gut the solid ascorbic acid particles present in the fat will be dissolved and absorbed as the fat is digested, it provides a positive nutrient effect as well as serving as an antioxidant. Furthermore, it is natural in its origin.

The Examples evidence the stabilization of a representative group of fats, oils, and carotenoids, as well as foods in which the fats or carotenoids are used. While extension of shelf life of foods is one objective of the invention, the reduction in degradation during present limited shelf storage is an even greater benefit, as it significantly improves the nutritional value of the food by delaying the development of fatty peroxides.

When formulated into a premix with carotenoids, the micron-sized ascorbic acid of the present invention acts both to stabilize the carotenoids and the fats in which they are dissolved or suspended when used in an animal feed. This result is not achieved effectively today even with available synthetic antioxidants.

Glossary of Terms

This glossary describes abbreviations and other technical terms and apparatus which may sometimes be referred to in this specification.

Abbreviation	Technical Term
BHA	butylated hydroxy anisole
BHT	butylated hydroxy toluene
GMO	glycerol mono-oleate
SO	soy oil
SMO	sorbitan mono-oleate
STO	sorbitan trioleate
SMS	sorbitan monostearate
8-1-0	octaglycerol mono-oleate
10-1-CC	decaglycerol mono-capric-caprylate
RM	rosemary extract, especially Herbalox-O™ product of Kalsec, Inc., Kalamazoo, Michigan

Peroxide Value: This is also a standard test for evaluation of the degree to which an oil has been oxidized.

Labiatae Extract: The solvent extract of a Labiatae herb, and preferably rosemary, sage, or thyme, especially rosemary. The preferable form is that described in Todd USP 4,877,635, and standardized to an antioxidant strength of about twice that of BHT in soy oil, under the standard Rancimat™ conditions. It is commercially available in the form of Herbalox™.

Rancimat™: An instrument which measures the induction time of an oleogenous substrate, usually at 120 degrees Celsius and at 18 liters of air per hour. This is an accepted methodology for determining relative strengths of preparations of antioxidants. The effectiveness is expressed as the induction time of the sample divided by the induction time of the control, as a percent.

2/3 life: This is the time it takes for 1/3 of the color of a sample of a food color, e.g., annatto, bixin, paprika, or other carotenoid or dispersed carotenoid oleoresin, to fade under the conditions of the experiment.

It is a highly-reproducible measurement, which is sufficiently accurate to evaluate the relative effectiveness of antioxidants and emulsifiers and synergistic combinations thereof. This technique will assist practitioners of the art to optimize formulations for specific uses.

Synergism: As defined in McGraw-Hill Dictionary of Scientific and Technical Terms: "An action where the total effect of two active components is greater than the sum of their individual effects." For example, if one additive increases the 2/3 life by 10 hours, and a second by 20 hours, and the combination of the two by 50 hours, the synergistic effect is an additional (or plus) 20 hours.

Surface-Active Agent: In the context of this specification, it represents a nonionic surface-active agent, especially one taken from the class consisting of:

a. mono and di glycerides of fatty acids,
b. polyglyceride esters of fatty acids,
c. mono and diglyceride esters further esterified with a dibasic organic acid taken from the class consisting of citric, lactic, and tartaric acids,
d. acetylated mono and diglyceride esters further esterified with a dibasic organic acid taken from the class consisting of citric, lactic, and tartaric acids,
e. sorbitan esters of fatty acids,
f. propylene glycol esters of fatty acids, and
g. lecithin, and equivalents thereof.

RM Rosemary Extract: The extract used is Herbalox^{tm}, which is a commercial product available from Kalsec, Inc., standardized as to antioxidant activity, and comprising about 20% active antioxidant compounds. It should be recognized, in this connection, that the art does not yet enable one to determine the exact concentration of active

antioxidants in the extract, and 20% is merely an approximation based on the degree of dilution of the deodorized rosemary extract with soy oil.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1 and 2 portray the fading curves of paprika and annatto pigments under controlled conditions. The percentage of the original color of the sample is plotted against time. Further details of the experiments are to be found in Example 4.

DETAILED DESCRIPTION OF THE INVENTION

The following Examples are given by way of illustration only, and are not to be construed as limiting.

These Examples show the preparation of the novel solid ascorbic acid antioxidant, its effectiveness by itself and in synergistic combinations with other antioxidants, and its use in preventing color loss with carotenoids. They portray its efficacy in a representative group of foods and feeds, as well as in essential oils and cosmetics, in such a manner that one skilled in the art may create forms of the invention best adapted to specific needs.

Where indicated, the Examples use a Rancimat^{tm} for the determination of the degree of stabilization of the substrate. This standard methodology involves blowing 18 liters of air per hour through a sample of an oil, measuring the conductivity in water of the gases generated, and determining when the oil has become rancid by the rate of change of conductivity. Higher temperatures are used for more stable oils, it being recognized that, for every ten degrees increase in temperature, the induction time decreases by about one-half. This standard methodology generates the same kind of induction curve as the standard TBA test. More sophisticated procedures, using chemiluminescence and electron spin resonance spectroscopy, show the

same pattern of oxidation. Accordingly, the stabilization of lipids with solid ascorbic acid reduces the rate at which toxic hydroperoxides form, and can contribute to the nutritional safety of our food supply.

Example 1 Preparation of Particles of Ascorbic Acid less than 38 Microns in Size (uAA), and Comparison of Antioxidant Activity with Prior Art.

The ascorbic acid of commerce is a white granular powder, similar in appearance to sugar but of smaller particle size. It is used as such, or impact milled to give a finer powder suitable for tableting. This powder has particles far greater than 38 microns in size on their largest dimension, usually about 180 microns on their largest dimension.

In the prior art applications, the mesh size of the ascorbic acid is not critical, since it is ultimately dissolved in water in the intended application as a nutrient and/or antioxidant. The only prior art advantage of finer powders is merely that of powdered sugar--the product is more compact, can be tableted more readily, and dissolves more quickly in the aqueous solution in which it is used as a nutrient or antioxidant.

In the new art described in this invention, the ascorbic acid is used as an antioxidant either per se or in a medium in which it is insoluble, and it is only effective in or out of such a medium if the particle size is less than about 38 microns. The mesh size is preferably below about 20 microns, and more preferably below 10 microns, with a substantial portion being below 5 microns. A solid ascorbic acid particle size wherein essentially all particles are 20 microns or less on their largest dimension is attainable and usually preferred.

<38 micron-sized ascorbic acid (uAA) may be prepared by grinding larger sized crystals (as in a mortar and pestle, or a hammer mill) and separating the <38 micron sized particles by sieving. Preferably, they are mixed with an oleogenous vehicle, in which the ascorbic acid is insoluble, and passed through a paint mill, or rolled as a suspension in oil in a pebble mill. Any of the other means of preparation of micron-sized particles known to the art are acceptable.

The micron-sized particles used in this and the following examples have, except where otherwise indicated, been prepared by pulverizing in a pebble mill in an oil. The particle size is best determined by observation under a microscope, and these preparations consist of essentially all particles being less than about 15 microns, with more than half being less than 5 microns in size on their longest diameter. The particle size may also be determined by sieving. All were less than 20 microns on their greatest dimension, and the particles had irregular shapes.

The product used in this example was prepared by adding one part of granular ascorbic acid (AA) to three parts of soy oil, and pebble milling for 72 hours to make the <38 micron sized particles (uAA).

TABLE 1.1

Comparative Antioxidant Power of Micron-Sized Ascorbic Acid in Soy Oil, a Medium in which it is Insoluble

Preparation	%Concentration of powder. uAA. BHA. or BHT in soy oil	Induction Time. Hours	Rancimat. 120°C. Ratio to Control
control	0	3.45	1.00
BHA	0.02	3.51	1.02
BHT	0.02	3.62	1.05
regular powder-AA	0.05	4.12	1.19
micron particles-uAA	0.05	10.22	2.88
ascorbyl palmitate	0.05	5.96	1.73

Discussion

If glycerol mono-oleate is substituted for soy oil as the vehicle for milling the particles, similar improvement in stability is observed.

In a similar test, at 113°C, the ratio of induction time of soy oil dosed with 0.005% uAA to the control was 1.38. This shows that the solid particles are effective at unconventionally low dose levels, far below the standard 0.02% permissible dose of oil-soluble synthetic antioxidants.

It is apparent that the <38 micron-sized ascorbic acid particles outperform even ascorbyl palmitate, an ascorbic fat-soluble ester of commerce, and that neither the commercial ascorbic acid nor the common synthetic antioxidants have significant effects. The uniqueness of this preparation is thus demonstrated.

Example 2 Dose Response of Canola Oil to <38 Micron-Size Ascorbic Acid Particles, and Comparison with Other Antioxidants.

Canola oil, a highly-unsaturated and widely-used vegetable oil, was dosed with varying amounts of the pebble-milled ascorbic acid of Example 1. Substantially all of the particles were below 20 microns in size, and most were below 10 microns in size. Additionally, the canola oil was dosed with several standard antioxidants at the commonly used level of 0.02%.

The stability of the oil was determined by the standard procedure on the Rancimat, at 110°C.

The dose level and stability in hours are reported in Table 2-1, as well as the ratio of the hours of the sample to the hours of the control.

TABLE 2-1

Stability of Canola Oil Dosed with Different Levels of <38 Micron-Size Ascorbic Acid Particles, and with Other Antioxidants.

Antioxidant	Dose, %	Stability hours	Ratio to control
control		9.24	1.00
uAA	0.001	9.80	1.06
uAA	0.002	11.64	1.26
uAA	0.005	12.25	1.32
uAA	0.01	14.55	1.57
uAA	0.01	14.75	1.59 with 0.01% rosemary
uAA	0.02	15.90	1.66
uAA	0.05	23.64	2.55
BHA	0.02	9.79	1.06
	0.20	10.07	1.09
BHT	0.02	9.79	1.06
AA palm.	0.02	12.50	1.35

Similar dose response curves are obtained with other fats.

The addition of rosemary at 0.01% shows a slight improvement. In a marine oil or animal fat, the improvement is greater.

Discussion

The Table shows that there is a continuous increase in stability with increasing amounts of the micron-sized ascorbic acid particles, and that they do not become a pro-oxidant at higher concentrations, as do certain other natural antioxidants. It also shows that the insoluble ascorbic acid particles are orders of magnitude more effective than several times the same amount of the most commonly-used synthetic antioxidants, BHA and BHT. It is surprising that the uAA is about four times as effective as its fatty acid ester.

It further points out that, to achieve a stability equivalent to that obtained by these synthetics at their dose limits of 0.02% in foods, less than 0.005% uAA and even as low as 0.001% or 0.002% uAA, may be used, although 0.02%, 0.05%, 1.0% uAA or above may be employed where desired or indicated. Exceptionally low doses are also shown to be effective in soy oil, cf. Example 1.

While oleogenous or lipid media such as soy oil are preferred suspending media for the uAA particles in the antioxidant composition of the invention, other suspending media in which the uAA particles are insoluble, such as hexane, may also be employed, especially where non-food use of the antioxidant composition is contemplated.

Example 3 Preparation and Use of Dry Micron-size Ascorbic Acid Particles in the Stabilization of Soy Oil.

Although the preferred procedure is to mill the ascorbic acid in a lipid medium, it can also be ground and directly added to the oil to be stabilized.

A commercial powdered ascorbic acid was ground in a mortar and pestle, and then selectively sieved through standard sieves to sort the particles according to their

largest diameter. Because of a tendency of the smallest particles to stick together, the larger mesh sizes contain some smaller mesh particles and, therefore, in the table below, the 30 to 38 micron fraction contains some 20 to 30 and some less than 20 micron particles. However, this does not affect the conclusion that smaller particles are preferred.

<20, 20-30, and 30-38 micron particles were dosed into soy oil at 0.05% w/w, and the induction times of the dosed oils compared to that of the control oil at 120°C., using the Rancimat. The ratios as compared to the control were 2.8, 2.2, and 2.0 respectively, showing that even the 30-38 micron is effective, but that the <20 micron is much superior.

A second experiment was performed in which soy oil was dosed at 0.05% with a commercial fine ascorbic acid powder, and with the sieved <20 micron particles. The particles suspended in the oil were then centrifuged in a standard lab centrifuge for thirty minutes, and the stability of the supernatant oils compared. The oil dosed with the commercial powder had the same stability as the control, showing no improvement due to the ascorbic acid. That containing the <20 micron particles had an induction time of 4.3 hours as compared to the 3.5 hours of the control, showing substantial improvement due to solid ascorbic acid particles remaining in suspension as a very slight haze.

In a third experiment, ascorbic acid particles less than 30 microns in size were obtained by sieving a mortared powder. A portion of the particles were wet with soy oil by agitation and degassing. Both the wetted portion and the dry particles were added to soy oil at 0.02% w/w, and the induction times determined on the Rancimat at 120°C. The difference between the induction times of the two test

samples and an undosed control was calculated, and it was found that the wetted particles were 128% as effective as the dry particles. This shows that the preferred form of the invention is wetted and degassed particles, which can be most easily obtained by wet milling.

Example 4 Stabilization of Paprika Pigments with Particles of Ascorbic Acid less than 38 Microns in Size, and Synergistic Mixtures with Other Natural Antioxidants. Stabilization of other Carotenoids.

Discussion

Paprika contains a mixture of carotenoid pigments, including hydrocarbons such as beta-carotene, and xanthophylls, such as capsanthin. Like any carotenoid, these substances are readily oxidized when exposed to air, and ethoxyquin is used by the art to stabilize them. Ethoxyquin is of questionable safety, and is not permitted as an antioxidant in any human food except paprika, where it may be used at levels of about 200 ppm. In animal feeds, it is permitted at 350 ppm.

Paprika pigments are fat soluble, and an extract, oleoresin paprika, is widely used in the food industry. Like ground paprika, this oleoresin fades rapidly when exposed to air and dispersed on a carrier, such as salt, dextrose, flour, and the like. A measure of effectiveness of an antioxidant is called the 2/3 life of the oleoresin when dispersed on flour salt, at a concentration of 2.7% of an oleoresin of 50,000 standard American Spice Trade Association color units. The 2/3 life is defined as the length of time required for 1/3 of the color to fade on a 2 gm. sample, held in a test tube at 65°C.

Example 4-1

In this example, the oleoresin paprika is stabilized

by adding an amount of a 25% suspension of <38 micron-sized ascorbic acid particles in soy oil, prepared by pebble milling the mixture of commercial powdered ascorbic acid and soy oil until the particles are less than 20 microns in size, and over half less than 10 microns in size.

This suspension is mixed thoroughly with the oleoresin paprika at a level of 5%, to give a concentration of 1.25% of the micron-sized ascorbic acid particles in the oleoresin.

To a portion of this mixture, a rosemary extract (RM), Herbalox (R), made by Kalsec, Inc., is added at a 2% level.

The 2/3 lives of the oleoresin dispersed on salt is measured by assaying the color on the salt in the test tubes, by the standard procedure of the American Spice Trade Association. (See Glossary.) They are reported in Table 4-1. Comparisons with standard synthetic oil-soluble antioxidants are shown. These include BHA, BHT, and ascorbyl palmitate (AP), a fat-soluble ester of ascorbic acid. Commercial ascorbic acid powder is also shown.

TABLE 4-1

2/3 lives of Oleoresin Paprika Containing Various Antioxidants

Preparation	% antioxidant(s)	2/3 Life hrs	increase hrs	syn hrs
Control		33		
BHT	0.2	35	2	
BHA	0.2	36	3	
AA commercial	1.25	36	3	
AP	0.6	55	22	
rosemary	2.0	64	31	
uAA	0.5	93	60	
uAA	1.25	203	170	
uAA + RM	1.25 + 2.0	336	303	102
uAA + GMO	1.25 + 6.25	247	214	
AA + GMO	1.25 + 6.25	36	3	

Discussion

Like BHA and BHT, the ascorbic acid of commerce gives the paprika a 2/3 life and color stability which is only

slightly higher than the control paprika. It is clear that only the micron-sized ascorbic acid particles have a dramatic effect, even though they are not soluble in the paprika. While the micron-sized ascorbic acid is exceptionally effective by itself, when combined with rosemary extract remarkable synergistic effects occur. The 102 hours color stability resulting from synergy is more than the hours gained by any of the other antioxidants, and is 330% of that added by the rosemary alone. This synergism is characteristic of other Labiatae extracts, such as those of sage and thyme. Such a Labiatae entirely natural system is many magnitudes better than any synthetic antioxidant, and it is particularly remarkable that the micron-sized ascorbic acid, which is insoluble in the oleoresin paprika and/or soy oil, is more effective than its fat-soluble ester, ascorbyl palmitate, and at a lower dose. The effectiveness and synergism are further enhanced by the addition of non-ionic emulsifiers, in which the ascorbic acid remains undissolved. In the above table, the effectiveness of glycerol mono-oleate (GMO) is shown. The commercial ascorbic acid was milled with GMO, and the micron-sized product added to the paprika oleoresin. The increase of 44 hours due to the GMO is significant. The range of utilizable emulsifiers includes the non-ionic surface-active agents mono- and di-glycerides of fatty acids, polyglyceride esters of fatty acids, mono- and di-glyceride esters further esterified with a dibasic organic acid taken from the class consisting of citric, tartaric, and lactic acids, sorbitan esters of fatty acids, and propylene glycol esters of fatty acids and especially mono- and di-glycerides, sorbitan fatty acid esters, glycerol mono-oleate, and mixed glycerol esters of fatty

acids, citric acid, and/or tartaric acid, with specific preferred emulsifiers being a monoglyceride of a fatty acid or a polyglycerol ester of a fatty acid and more specifically, glycerol mono-oleate or decaglycerol capric-caprylate, some especially preferred nonionic surface-active agents being GMO, STO, SMO, SMS, 8-1-0, and 10-1-CC. Such surface-active agents can be advantageously included in any of the antioxidant compositions of the invention, and even to produce synergistic effects, as further disclosed and illustrated herein.

The same improvement over the prior art antioxidants is exhibited with other carotenoids, such as bixin, carrot extract, beta-carotene, and other synthetic carotenoids such as canthaxanthin, astaxanthin, and beta-apo-8-carotenal which are presently stabilized by encapsulation in gelatin.

Example 4-2

For example, the 2/3 life of a 1.35% w/w dispersion on flour salt of a 5% microcrystalline suspension of bixin was increased from 18 hours to 186 hours by the addition of 1.25% w/w of <38 micron-size ascorbic acid particles milled in glycerol mono-oleate (GMO) as prepared above. Activated ascorbic acid prepared according to my copending application, by dissolving the ascorbic acid in methanol, mixing with GMO, and desolventizing, gave a 2/3 life of 146 hours. This is significantly below the stability achieved with the uAA. The addition of rosemary extract further extends the 2/3 life. As in the case of paprika oleoresin, the commercial ascorbic acid powder is without effect, and the synthetic antioxidants are substantially less effective than the micron-sized ascorbic acid composition.

FURTHER REFERENCE TO THE DRAWINGS

FIGS. 1 and 2 show the fading curves of the above two

carotenoids, and assist in visualization of the statements and data in the foregoing.

FIG. 1 shows that the control A, paprika (in soy oil), as well as B, paprika in soy oil with normal ascorbic acid particles, and C, paprika in glycerol mono-oleate, faded rapidly and had a 2/3 life of less than 56 hours, whereas the paprika in soy oil in the presence of the micron-sized ascorbic acid of the present invention had a 2/3 life in excess of 200 hours (203 hours) which could be further substantially extended (to 247 hours) by the inclusion of glycerol mono-oleate in the suspension with the micron-sized ascorbic acid particles.

FIG. 2 shows the rapid fading of annatto pigments such as bixin in soy oil, much less rapid fading of such pigments in glycerol mono-oleate containing the micron-sized ascorbic acid particles according to the invention and a substantially shorter 2/3 life when the activated ascorbic acid dissolved in glycerol mono-oleate according to my prior invention is employed, the 2/3 lives being 18 hours, 186 hours, and 146 hours, respectively.

From the above, it is clear that the <38 micron-size ascorbic acid particles are effective antioxidants for carotenoids, even though insoluble in the preparation. Furthermore, it is clear that synergistic effects are attained when the <38 micron-size ascorbic acid is combined with a natural antioxidant, such as rosemary, thyme, or sage, and that the effects are preserved or enhanced in the presence of non-ionic emulsifiers. Tea extract or tocopherol or other natural antioxidant may be used in place of rosemary with only slight disadvantage, e.g., lesser antioxidant power and/or discoloration as noted elsewhere herein. All of this is new to the art.

Example 5 Stabilizing the Color of Seasoned Potato Chips.

Potato chips were prepared commercially, and 25 gms were placed in paper bags. To these bags were added 5 gms of salt upon which 3.3% of a 40,000 color value oleoresin paprika had been predispersed. The oleoresin contained the levels of rosemary (RM) extract (Herbalox^{tm}), tocopherols (T), <10 micron ascorbic acid particles (uAA), and soy lecithin noted in Table 4-1. In this case, the uAA was obtained by milling and was at a concentration of 26% by weight in soy oil. The samples which contained no lecithin did contain the equivalent amount of soy oil, which is commonly used as a standardization medium. Each sample was completely mixed. Preferably, the additives are also premixed and then added, but they can be added individually as well.

The colored potato chips were placed in clear plastic bags under fluorescent light of the quality used in food stores. They were exposed for two weeks at room temperature. Another portion of the chips was kept in the dark.

The chips stored in the light were then evaluated for color fading, aroma, and taste.

The results are as shown below.

TABLE 5-1

Composition and Stability of Colored Potato Chips.

Composition of Oleoresin %							
RM	T	uAA	Lecithin	color	aroma	taste	acceptability
0	0	0	0	faded	rancid	rancid	reject
3	0	3	0	stable	fresh	oily	acceptable
3	0	3	25	stable	sl off	sl off	acceptable
3	2.6	3	25	stable	sl off	sl off	acceptable

The color of the control did not fade as much in the dark, but the flavor ranking of the sample was similar to the 0000 sample exposed to the light.

It is clear that all of the combinations containing uAA held their color, while the control did not. The slightly off aromas of the samples containing lecithin were described as oily-nutty, and it should be noted that the addition of tocopherol did not effect the development of this defect. Although not shown, it is known that the rosemary extract by itself would improve the color and flavor stability. However, the combination thereof with micron-sized particles of ascorbic acid is synergistic in the improvement of stability.

Although the color of ground paprika is more stable than that placed on potato chips, it does fade when stored at room temperature. It may be stabilized in the same fashion as the oleoresin, by adding a premix consisting of the uAA in an oleogenous vehicle in which it is insoluble, such as partially hydrogenated fats, mono-diglycerides, lecithin, and the like.

Such a premix preferably contains a rosemary, sage, or thyme extract, to achieve synergistic stabilizing effects.

Example 6 Particle Size Distribution of Pebble-Milled Ascorbic Acid in Soy Oil.

Commercial ascorbic acid powder was pebble milled for 96 hours, at a concentration of 26% w/w in soy oil. The size of the particles was determined by admixing 10 g of the preparation with 100 ml of hexane and passing this through 38, 30, and 20 micron-sized screens with agitation, while rinsing the particles through the screens with solvent. Any particles larger than the mesh size of the screen are retained on the screen with such a procedure. Less than 0.1% of the weight of the ascorbic acid particles was retained on any screen, showing that more than 99% was less than 20 microns in size.

A representative portion of the particles passing the 20-micron screen was mixed with castor oil, placed on a microscope slide, and examined using a lens piece which permits sizing of the particles. The particles in twelve random fields were counted according to size, and it was found that 84% were less than 5 microns, 13% between 5 and 10 microns, and 3% between 10 and 20 microns. The particles had irregular shapes. No commercial preparation of ascorbic acid is known which has such a concentration of less than 20-micron sized particles.

The same particle-size distribution may be obtained with lesser and greater percentages of ascorbic acid in the medium, e.g., in the oleogenous medium. As the concentration becomes greater, the suspension becomes thicker and more difficult to mix into the material to be stabilized. Concentrations up to about 35% are preferred, but higher concentrations are within the scope of this invention. Lower concentrations, such as 1% or 5%, are practical but less advantageous because the additional medium serves little useful purpose. It is the ascorbic acid particles per se or suspended in a medium in which they are insoluble which is the operative antioxidant and anti-fading component, and the concentration is incidental except in the ultimate vehicle which is to be stabilized.

It should be noted that the particles all had irregular surfaces and shapes, indicating fracture and exposure of surfaces to the medium in which it was milled. It is believed that this increases effectiveness of the particles, as well as their ability to be wet by the milling medium, thereby increasing their effectiveness as compared with a dry powder added directly to the oil to be stabilized.

The milling medium is not critical, although preferably oleogenous, provided that it does not dissolve the solid ascorbic acid particles, and need only be compatible with the oil or food to be stabilized, and edible when intended for use in a product to be ingested. Likewise, the concentration of ascorbic acid in the vehicle is not critical, although preferred levels are between about 10% or 20% and 35%, and practical levels range from 5% to 50%.

Example 7 Stabilization of Chicken Fat with the Ascorbic Acid Suspension of Example 6, and Mixtures Thereof with Sage Extract.

Chicken fat was rendered from a whole carcass, separated from the broth, filtered, and dosed as shown in Table 7-1. The sage extract was Herbalox (R), Type S, made by Kalsec. It, like rosemary, is representative of the antioxidant power of Labiatae extracts.

The synergistic effect of the combination of sage and uAA should be noted, since the uAA increases the effectiveness of the sage by (6.64-1.81)/(2.59-1.00) = 4.83/1.59 = 300%. Tocopherols at doses as low as 0.02% also are highly effective in combination with uAA, and in combination with uAA plus rosemary.

TABLE 7-1

Induction Times and Ratios to Control of Chicken Fat Stabilized with uAA, and with uAA plus Sage Extract.

	dose	induct, hrs	ratio to control
control	0	0.80	1.00
uAA	0.02	2.07	2.59
sage	0.02	1.45	1.81
uAA + sage	0.02 + 0.02	5.31	6.64

Turkey fat, another poultry fat, responds like chicken. Benefits obtained with pork and beef fats as

substrates are similar. Where paprika, either ground or as an oleoresin, is combined with the fat-containing meat to make a sausage, the benefit of stabilization of the fat and carotenoid is combined. Rancidity is retarded by adding the uAA to fresh poultry meat, particularly in combination with Labiatae extracts.

Example 8 Stabilization of Pigmented Fish Food.

Discussion

The farming of trout and salmon has created a substantial market for manufactured feed which contains pigments which will color the flesh of the fish. Likewise, the need for highly-colored egg yolks has provided a market for both yellow and more orange pigments. Among those carotenoids now being used are canthaxanthin, astaxanthin, marigold xanthophylls, and paprika xanthophylls.

The animal diets contain fats, which should also be stabilized to provide optimal nutritional value (for example, salmon grow poorly when fed oxidized fats). This invention provides a means of stabilizing the fat and the pigment at the same time. Vitamin A, being related to the carotenoids, is also stabilized.

In this invention, pelleted trout food is made in the normal manner by extrusion, and it is then coated with a fat to which the premix of carotenoid, antioxidant, and optional emulsifier or bodying agent has been added. The carotenoid may be either in its free or esterified form. Although marine oils may be used successfully, they are less preferred than more saturated oils.

Example

A control mixture of 30% oleoresin paprika and 70% soy oil was made. A second test mixture containing 30% oleoresin paprika, 6% rosemary extract, 14% of the uAA of

Example 6, and 50% soy oil , and a third test mixture consisting of 30% oleoresin paprika, 6% of rosemary extract, 14% of the uAA, and 50% lecithin were prepared. The stability of the oleoresins was evaluated on the Rancimat at 110°C/18 liters air/hr. Conductivity rather than induction time was used to measure stability, with the control having a conductivity of 222 and the test sample without lecithin a conductivity of 65 at the end of 17 hours. This shows the effectiveness of uAA. The lecithin sample foamed and conductivity could not be determined. The control sample had faded, the lecithin sample had become brownish, and the sample with only uAA and rosemary remained a bright red.

The 2/3 lives of the color was also determined by placing 1 g samples in test tubes in an oven at 80°C. Since foaming could not occur, the 2/3 lives of all samples could be ascertained: control,79 hours; uAA + rosemary, 132 hours; and uAA + rosemary + lecithin, 161 hours. The lecithin-containing sample had become brownish, the control orangish, and the uAA + rosemary retained a bright red color. This demonstrates that lecithin may be used in such a premix, but that it may cause discoloration.

This specific premix formula is not intended to be limiting, since more or less of the ingredients can be included. Only the uAA is essential to the stabilization of the color, but the rosemary or other Labiatae extract has a positive impact. Tea extract is another natural extract which may be used. Other antioxidants, such as ethoxyquin normally found in fish oils at 350 ppm, are compatible. Chelating agents, such as citric acid, may be useful if metal content is a problem.

Example 9 Stabilization of a Marine Oil.

Salmon oil was dosed with the 0.05% uAA of Example 6; with 0.05% uAA and 0.075% lecithin; and with 0.075% lecithin alone. At 95°C, the ratios of the induction times to the control, of the respective samples, were 1.98, 2.63, and 1.41. This shows that lecithin is compatible with uAA in a marine oil, where it also functions as an antioxidant. There is a slight synergistic effect.

Example 10 Stabilization of Essential Oils and Cosmetics.

Although the present invention is especially adapted to foods containing fats, it also has utility for the stabilization of essential oils. For example, orange oil was dosed with 0.05% of the uAA of Example 6, agitated one week in a loosely-closed container, and compared with the original oil which was undosed, but similarly exposed to oxidation. The control oil had developed a noticeable sharp, aldehyde-like aroma typical of oxidized orange oil. The dosed sample had not. Other oils high in hydrocarbons, such as black pepper, peppermint, dill, and lemon are particularly well stabilized by this invention.

If an essential oil is incorporated into a cosmetic, particularly into the fatty phase of a cosmetic like a cream or lipstick, both the essential oil and the fat are stabilized by the uAA. Even castor oil can benefit from the addition of this ascorbic acid composition.

Example 11 Further Illustration of Stabilized Foods.

Peanut butter is subject to oxidative degradation, having a shelf life of less than a year. Peanut butter was made in the conventional manner, without antioxidants, with 0.02% BHT, with 0.02% rosemary, and with 0.02% rosemary and .04% uAA of less than 38 microns in size. Peroxide values

were determined on the fat after two months of storage at 85°F. The results were, respectively, 18.0, 10.4. 18.8, and <1. The uAA obviously had a tremendous effect, and the rosemary alone was without effect in this particular substrate.

The stability of safflower oil, which is highly unsaturated like peanut oil, also greatly benefits from the addition of uAA.

* * * * *

It is thus seen that the present invention provides a novel and advantageous form of solid particulate ascorbic acid and antioxidant compositions thereof, such products having increased antioxidant activity in fats, oils, carotenoids, and fatty foods, especially such materials and products as are exposed to oxidative stress, as well as a method of stabilizing such materials and products against oxidative discoloration, feeds and foodstuffs which may encounter oxidative stress stabilized with a composition of the invention, and a method of stabilizing a feed or foodstuff or flavoring with such a more effective form of ascorbic acid and/or ascorbic acid antioxidant composition of the invention. The stabilization of carotenoid pigments may thus advantageously be carried out. Synergistic effects are obtained by the incorporation of a natural antioxidant, e.g., such a fat- or oil-soluble antioxidant, in such compositions, methods, and products, and the antioxidant effectiveness of the antioxidant, antioxidant compositions, and methods of the invention is further enhanced by inclusion of a natural Labiatae antioxidant, tea extract, or a tocopherol therein, and antioxidant power and stabilization effectiveness may be even further improved by inclusion therein of a nonionic surface-active agent. All of the foregoing provide long-awaited solutions

to previously-existing oxidation and instability problems not adequately solved by the prior art.

I claim:

- 1 -

An antioxidant composition consisting essentially of solid particles of ascorbic acid which are less than about 38 microns in size on their largest dimension, preferably wherein at least about 50% of the solid particles of ascorbic acid are less than about 10 microns in size on their largest dimension, especially wherein essentially all of the particles are about 20 microns or less on their largest dimension.

-2-

An antioxidant composition consisting essentially of a suspension of solid ascorbic acid particles in a medium in which they are insoluble, the solid particles of ascorbic acid being less than about 38 microns in size on their largest dimension, preferably wherein at least about 50% of the solid particles of ascorbic acid are less than about 10 microns in size on their largest dimension, especially wherein at least about 50% of the solid particles of ascorbic acid are less than about 5 microns in size on their largest dimension, preferably wherein essentially all of the particles are about 20 microns or less on their largest dimension, preferably wherein the concentration of ascorbic acid particles in the medium is between about 5% and about 50% by weight, and especially wherein the ascorbic acid particles have irregular shapes and their concen-

tration in the medium is between about 20% and 35% by weight.

- 3 -

The method of preparing an antioxidant composition consisting of the step of grinding solid ascorbic acid particles to a size less than about 38 microns on their largest dimension in a medium in which they are insoluble, preferably wherein at least about 50% of the solid particles of ascorbic acid are ground to a size less than about ten microns on their largest dimension, especially wherein at least about 50% of the solid particles of ascorbic acid are ground to a size less than about five microns on their largest dimension, preferably wherein essentially all of the ascorbic acid particles are ground to a size of about twenty microns or less on their largest dimension, especially wherein the concentration of ascorbic acid particles, ground to a size less than about 38 microns on their largest dimension, in the medium is between about 5% and about 50% by weight, and preferably wherein the ascorbic acid particles are ground into irregular shapes and their concentration in the medium is between about 20% and about 35% by weight.

- 4 -

The method of protecting an edible or other fat, oil, carotenoid, fatty food, or other substrate which is lipid in nature or which comprises a lipid phase, comprising the step of admixing the said substrate with an oxidation-protective amount of a composition of Claim 1 or 2, especially wherein the medium is oleogenous, preferably by the addition thereto of at least about 0.002% by weight of solid ascorbic acid particles which are less than about 38 microns in size on their largest dimension, especially wherein the protected substrate comprises a member selected

from the group consisting of: soy oil; canola oil; peanut oil; sunflower oil; chicken fat; pork fat; turkey fat; beef fat; a marine oil; a paprika carotenoid; an annatto carotenoid; canthaxanthin; astaxanthin; and beta-carotene, and preferably wherein the amount of the oxidation-protective composition employed is calculated to provide an amount of microcrystalline ascorbic acid in the substrate of at least about 0.002% by weight.

- 5 -

A fat or oil composition, optionally containing a carotenoid, which is protected from oxidative degradation by a suspension of 0.001% or more, preferably .002% or more, by weight of an antioxidant composition consisting essentially of solid ascorbic acid particles, having a size less than about 38 microns on their largest dimension, preferably a suspension thereof in a medium in which they are insoluble, preferably wherein at least about 50% of the solid particles of ascorbic acid are less than about 10 microns in size on their largest dimension, especially wherein at least about 50% of the solid particles of ascorbic acid are less than about 5 microns in size on their largest dimension, especially wherein the solid particles of ascorbic acid are 20 microns or less in size on their largest dimension, especially wherein the concentration of ascorbic acid particles of less than about 38 micron size in the medium when present is between about 5% and about 50% by weight, and preferably wherein the concentration of ascorbic acid particles of less than about 38 micron size in the medium when present is between about 10% and 35% by weight.

- 6 -

A food or feed which is lipid in nature or which comprises a lipid phase in which the lipid or lipid phase

is stabilized with an oxidation-protective amount of a composition of Claim 1 or 2, preferably wherein the medium is oleogenous, especially wherein the amount of the composition employed is calculated to provide an amount of microcrystalline ascorbic acid in the food or feed of above about 0.001% by weight, preferably wherein the food or feed is protected with at least about 0.002% by weight of solid microcrystalline ascorbic acid particles, especially wherein the food or fat comprises a member selected from the group consisting of: soy oil; canola oil; peanut oil; sunflower oil; chicken fat; pork fat; turkey fat; beef fat; a marine oil; a paprika carotenoid; an annatto carotenoid; canthaxanthin; astaxanthin; and beta-carotene, and preferably wherein the amount of microcrystalline ascorbic acid in the medium is at least about 0.005% by weight.

- 7 -

The method of stabilizing the fatty phase of a cosmetic or an essential oil by admixing the fat with an oxidation-protective amount of an antioxidant composition consisting essentially of ascorbic acid particles which are less than about 38 microns in size on their longest dimension, optionally suspended in a medium in which they are insoluble.

- 8 -

The method of stabilizing Vitamin A by admixing the Vitamin A with an oxidation-protective amount of an antioxidant composition consisting essentially of ascorbic acid particles which are less than about 38 microns in size on their longest dimension, optionally suspended in an edible medium in which they are insoluble.

- 9 -

A composition or product or method of any preceding claim wherein the antioxidant composition or oxidation-

protected or stabilized product comprises also a natural oil-soluble antioxidant, preferably one taken from the class consisting of Labiatae extracts, tea extracts, and tocopherols.

- 10 -

The antioxidant composition or method or oxidation-protected or stabilized product of any preceding claim wherein a medium is employed, wherein the medium is an edible oleogenous medium.

- 11 -

The antioxidant composition or method or oxidation-protected or stabilized product of any preceding claim, wherein the antioxidant composition comprises also a non-ionic surface-active agent, preferably an orally-ingestible non-ionic surface-active agent, and preferably one selected from the group consisting of

a. mono and di glycerides of fatty acids,

b. polyglyceride esters of fatty acids,

c. mono and diglyceride esters further esterified with a dibasic organic acid taken from the class consisting of citric, lactic, and tartaric acids,

d. acetylated mono and diglyceride esters further esterified with a dibasic organic acid taken from the class consisting of citric, lactic, and tartaric acids,

e. sorbitan esters of fatty acids,

f. propylene glycol esters of fatty acids, and

g. lecithin, and preferably a surface-active agent comprising glycerol mono-oleate, sorbitan trioleate, sorbitan mono-oleate, sorbitan monostearate, octaglycerol mono-oleate, or decaglycerol capric caprylate.

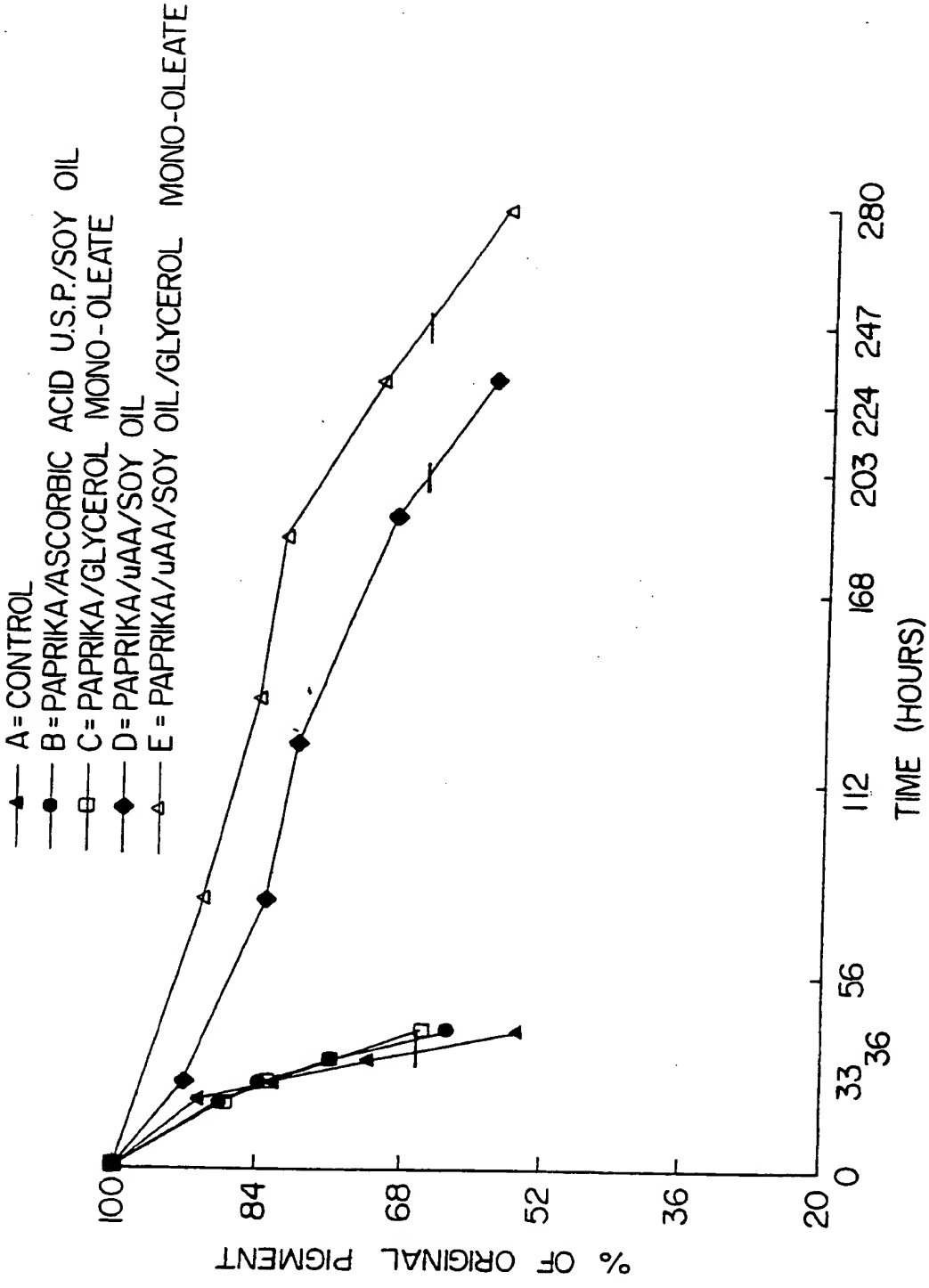
A = CONTROL
B = PAPRIKA/ASCORBIC ACID U.S.P./SOY OIL
C = PAPRIKA/GLYCEROL MONO-OLEATE
D = PAPRIKA/uAA/SOY OIL
E = PAPRIKA/uAA/SOY OIL/GLYCEROL MONO-OLEATE
% OF ORIGINAL PIGMENT
100
84
68
52
36
20
0
33
36
56
112
168
203
224
247
280
TIME (HOURS)

FIG. 1

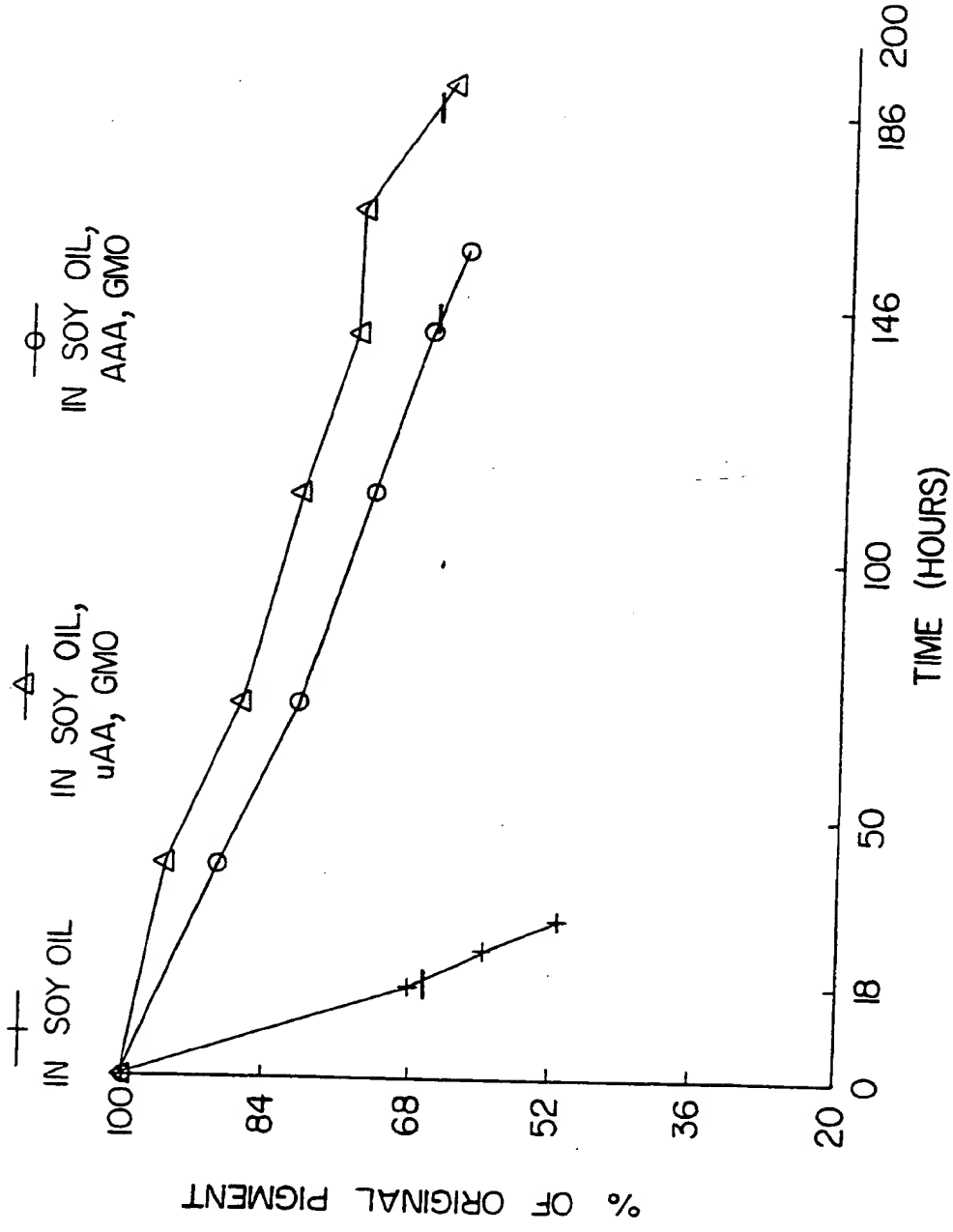
% OF ORIGINAL PIGMENT
100
84
68
52
36
20
0
18
50
100
146
186
200
TIME (HOURS)
IN SOY OIL
IN SOY OIL, uAA, GMO
IN SOY OIL, AAA, GMO

FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/04874

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :IPC(5) A23B 4/00;
US CL :US 426/451,252/389
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : US 426/451,252/389

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A, 3966632 (Colliopoulos et al.) 29 June 1967 See col. 1, lines A2-58 and 67-68	1-11
Y	US,A, 4,352,746(Bracco et al.) 05 OCTOBER 1982 see col. 5, lines 28-34 and 40	1-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 15 SEPTEMBER 1992	Date of mailing of the international search report 20 NOV 1992
Name and mailing address of the ISA/ US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer VALERIE FEE NGUYEN NGOC-HO INTERNATIONAL DIVISION Telephone No. (703) 308-0441

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/27433

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 7/42, 7/44
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

USPATFULL online
CAS online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,505,935 A (GUERRERO et al) 09 April 1996, columns 5 and 6 inclusive.	1-58

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 01 MARCH 1999	Date of mailing of the international search report 16 MAR 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JAMES O. WILSON Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

Panthenol	0.2
Total	**100%**

58. Any of the compositions of claim 56, further comprising a suncreen agent, and apolyorganosiloxane water-in-oil emulsion that increases an SPF of the composition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/27433

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

424/59, 60
514/ 772, 772.3, 772.4, 844, 847, 937, 938

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

424/59, 60
514/ 772, 772.3, 772.4, 844, 847, 937, 938

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/BR 00072

International Application No.

03 SET 1999 03-9-99

International Filing Date

INPI, BRAZIL - PCT INTERNATIONAL APPLICATION

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* PE-3638

Box No. I TITLE OF INVENTION

"Process and composition for enhancing the action of vitamin A on the cellular activity of an individual, and use of vitamin C"

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

INDÚSTRIA E COMÉRCIO DE COSMÉTICOS NATURA LTDA.
Rodovia Regis Bittencourt S/N - KM 293
06850 - Itapecerica da Serra - SP
Brazil

☐ This person is also inventor.

Telephone No.
(55 11) 7940-1133

Facsimile No.
(55 11) 7940-1094

Teleprinter No.

State *(that is, country)* of nationality: BR

State *(that is, country)* of residence: BR

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ALCANTARA MARTINS ZUCCHETTI, ROBERTO
Rua Serra do Japi, 242, apto. 23B
Tatuape
03309-000 - São Paulo - SP
Brazil

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: BR

State *(that is, country)* of residence: BR

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

DANNEMANN, SIEMSEN, BIGLER & IPANEMA MOREIRA
Caixa Postal 2142
Rua Marquês de Olinda, 70
Botafogo
22251-040 - Rio de Janeiro - RJ
Brazil

Telephone No.
(21) 553.1811

Facsimile No.
(21) 553.1812
553.1813

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

PCT/BR 97/00072

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

CHITARRA SOUZA, SIMONI
Rua Estela 22, apto. 331
Vila Mariana
São Paulo - SP
Brazil

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: BR

State *(that is, country)* of residence: BR

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

VILLA NOVA SILVA, LUCIANA
Rua Américo Alves Pereira Filho, 564
Morumbi
05688-000 - São Paulo - SP
Brazil

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: BR

State *(that is, country)* of residence: BR

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

- [ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- ☐ **AP** **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☐ **EA** **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☐ **OA** **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☐ **AE** United Arab Emirates
- ☐ **AL** Albania .....
- ☐ **AM** Armenia .....
- ☐ **AT** Austria .....
- ☐ **AU** Australia .....
- ☐ **AZ** Azerbaijan
- ☐ **BA** Bosnia and Herzegovina .....
- ☐ **BB** Barbados
- ☐ **BG** Bulgaria .....
- ☐ **BR** Brazil .....
- ☐ **BY** Belarus .....
- ☒ **CA** Canada
- ☐ **CH and LI** Switzerland and Liechtenstein
- ☐ **CN** China .....
- ☐ **CU** Cuba .....
- ☐ **CZ** Czech Republic .....
- ☐ **DE** Germany .....
- ☐ **DK** Denmark .....
- ☐ **EE** Estonia .....
- ☐ **ES** Spain .....
- ☐ **FI** Finland .....
- ☐ **GB** United Kingdom
- ☐ **GD** Grenada
- ☐ **GE** Georgia .....
- ☐ **GH** Ghana .....
- ☐ **GM** Gambia
- ☐ **HR** Croatia .....
- ☐ **HU** Hungary .....
- ☐ **ID** Indonesia
- ☐ **IL** Israel .....
- ☐ **IN** India .....
- ☐ **IS** Iceland
- ☒ **JP** Japan .....
- ☐ **KE** Kenya .....
- ☐ **KG** Kyrgyzstan .....
- ☐ **KP** Democratic People's Republic of Korea .....
- ☐ **KR** Republic of Korea .....
- ☐ **KZ** Kazakhstan .....
- ☐ **LC** Saint Lucia
- ☐ **LK** Sri Lanka
- ☐ **LR** Liberia
- ☐ **LS** Lesotho .....
- ☐ **LT** Lithuania
- ☐ **LU** Luxembourg
- ☐ **LV** Latvia
- ☐ **MD** Republic of Moldova .....
- ☐ **MG** Madagascar .....
- ☐ **MK** The former Yugoslav Republic of Macedonia .....
- ☐ **MN** Mongolia
- ☐ **MW** Malawi .....
- ☒ **MX** Mexico .....
- ☐ **NO** Norway
- ☐ **NZ** New Zealand .....
- ☐ **PL** Poland .....
- ☐ **PT** Portugal .....
- ☐ **RO** Romania
- ☐ **RU** Russian Federation .....
- ☐ **SD** Sudan
- ☐ **SE** Sweden
- ☐ **SG** Singapore
- ☐ **SI** Slovenia .....
- ☐ **SK** Slovakia .....
- ☐ **SL** Sierra Leone .....
- ☐ **TJ** Tajikistan .....
- ☐ **TM** Turkmenistan .....
- ☐ **TR** Turkey .....
- ☐ **TT** Trinidad and Tobago .....
- ☐ **UA** Ukraine .....
- ☐ **UG** Uganda .....
- ☒ **US** United States of America .....
- ☐ **UZ** Uzbekistan .....
- ☐ **VN** Viet Nam .....
- ☐ **YU** Yugoslavia .....
- ☐ **ZA** South Africa .....
- ☐ **ZW** Zimbabwe .....

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☐ .....
- ☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

PCT/BR 99/00072

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 8 September 1998 (08.09.98)	PI 9803936-9	BR		
item (2)				
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): _____

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*: ISA / EPO

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:
Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	:	4
description (excluding sequence listing part)	:	6
claims	:	2
abstract	:	1
drawings	:	1
sequence listing part of description	:	–
Total number of sheets	:	14

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☒ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☒ priority document(s) identified in Box No. VI as item(s): 1
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other *(specify)*: Inventors' assignment

Figure of the drawings which should accompany the abstract: 1 and 2

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Dannemann, Siemsen, Bigler & Ipanema Moreira

For receiving Office use only

1. Date of actual receipt of the purported international application: 03 SET 1999 03-9-99
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET
Annex to the Request

For receiving Office use only

International application No. PCT/BR 99/00072

Date stamp of the receiving Office

Applicant's or agent's file reference: PE-3638

Applicant: INDUSTRIA E COMERCIO DE COSMETICOS NATURA LTDA., ALCANTARA MARTINS ZUCCHETTI, ROBERTO, CHITARRA SOUZA, SIMONI and VILLA NOVA SILVA, LUCIANA

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . R$ 236,00 [T]

2. SEARCH FEE DM. 550. x 1,053630 . . . . . R$ 579,50 [S]

International search to be carried out by EPO

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 14 sheets.

first 30 sheets CHF 650x1,289160 . . . R$ 837,95 [b1]

___ (remaining sheets) x ___ (additional amount) = - [b2]

Add amounts entered at b1 and b2 and enter total at B . . . . R$ 837,95 [B]

Designation Fees

The international application contains 5 designations.

5 (number of designation fees payable *(maximum 11)*) x CHF 150x1,289160 (amount of designation fee) = R$ 966,87 [D]

Add amounts entered at B and D and enter total at I . . . . . R$ 1.804,82 [I]

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . - [P]

5. TOTAL FEES PAYABLE . . . . . R$ 2.620,32 TOTAL

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☐ authorization to charge deposit account (see below)	☐ bank draft	☐ coupons
☐ cheque	☒ cash	☐ other *(specify)*:
☐ postal money order	☐ revenue stamps	

DEPOSIT ACCOUNT AUTHORIZATION *(this mode of payment may not be available at all receiving Offices)*

The RO/ _____

☐ is hereby authorized to charge the total fees indicated above to my deposit account.

☐ is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

Deposit Account No. _____ Date *(day/month/year)* _____ Signature _____

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

DANNEMANN, SIEMSEN, BIGLER
& IPANEMA MOREIRA
Rua Marqués de Olinda, 70
Botafogo
22251-040 - Rio de Janeiro - RJ
BRESIL

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	06.12.2000
Applicant's or agent's file reference PE-3638	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/BR99/00072	03/09/1999	08/09/1998

Applicant
INDUSTRIA E COMERCIO DE COSMETICOS NATURA LTDA.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Tantum, P Tel.+49 89 2399-8143

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PE-3638		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/BR99/00072	03/09/1999	08/09/1998

International Patent Classification (IPC) or national classification and IPC
A61K7/48

Applicant
INDUSTRIA E COMERCIO DE COSMETICOS NATURA LTDA.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07/04/2000	06.12.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Grillenberger, S Telephone No. +49 89 2399 8938

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/BR99/00072

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-6 as originally filed

Claims, No.:

1-6 as received on 23/10/2000 with letter of 18/10/2000

Drawings, sheets:

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-6
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-6
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D5: EP-A-0 781 551 (ADVANCED POLYMER SYSTEMS INC) 2 July 1997 (1997-07-02)
D6: EP-A-0 229 561 (MOET HENNESSY RECH) 22 July 1987 (1987-07-22)

1.1 D5 describes "solid porous particles in whose pores the retinoid compositions are retained" (p.3, l.44), said retinoid skin care compositions (p.2, l.6) comprising "both naturally occurring and synthetic compounds bearing the general structure of Vitamin A and variations on that structure which bear similarities to retinol in terms of biological activity" (p.2, l.43 to p.3, l.13), and "additional ingredients (...) to further enhance the stability and usefulness of the retinoid compound" (p.3, l.21). One type of additional ingredient are antioxidants, e.g. α-tocopherol (Vitamin E) (p.3, l.27), or ascorbic acid (Vitamin C) (p.3, l.2). In Examples I-III (p.5, top to p.6, l.21), both Vitamin E and Vitamin C are used in combination with Vitamin A.
D5 also states that "skin irritation due to retinoids can be reduced and stability can be increased by formulating the retinoids as particles or particle suspensions" (p.2, l.25).

1.2 D6 discloses dermatological compositions on the basis of liposomes containing a retinoid or other carotenoid structural analogue (p.2, l.1-3), which allow potentiation of efficacy concommitantly with reduction of toxic effects (p.2, l.45). The liposomes of Example 12 of D6 contain an "antioxidant liposoluble" (p.11, l.25; in Examples 1-10, this is α-tocopherol) and ascorbic acid together with "Trétinoine", the Vitamin A analogue.

2. Novelty: Art.33(1 and 2) PCT
None of the relevant prior art discloses formulations based on **two groups** of micro-spheres, with Vitamin A and Vitamin C therefore contained in separate compartments. Hence, the subject-matter of present Claims 1-6 is considered to be novel.

3. Inventive Step: Art.33(1 and 3) PCT

Both D5 and D6 may be considered as closest prior art, since both disclosures solve the technical problem of the present invention, which is to allow application of Vitamin A in efficient yet tolerably low concentrations by enhancing its activity with additional Vitamin C. The present invention employs Vitamin A and Vitamin C in separate micro-compartments, but still in one and the same formulation (Description p.5, l.24ff.). Inevitably, the active agents are **applied to the skin together**. Therefore, the present invention is merely an alternative to the state of the art, and does not confer any new and/or unexpected technical effect.
For this reason, the present subject-matter cannot be considered to be inventive.

4. For the assessment of the present claims 1-6 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the international application

Concerning Claim 2, it is assumed that the first sentence should read "...characterized in that Vitamin C is present at a **concentration** of..."

Re Item VIII

Certain observations on the international application

The statement concerning an advantageous technical effect of the invention ("possible (for the vitamins) to **reach the deeper layers of the skin** in (...) integrity"), which was introduced into the Description (p.5 top) by the Applicant with letter of 18.10.2000 is not deducible by a person skilled in the art from the application as filed, and therefore does not fulfill the requirements of Art.34(2b) PCT and PCT-Guidelines III.7.12b.

The introduction of Vitamins C, A and E in microspheres increases their action and makes it possible for them to reach the deeper layers of the skin with greater, or even total, integrity, without degeneration of the product in the path between the application area and the place of action.

In a particularly preferred way, the cosmetic compositions according to the present invention are formulated in such a manner, that their components are contained in organic vectors such as microspheres and, more particularly, in microspheres or microcapsules containing biologically active material ("Talasferas") such as those defined in US Pat 5,395,620, or in Brazilian patent application PI 9706994-7, filed in the name of this same applicant.

The composition as described above may contain a plurality of said microspheres, in a dispersed form, comprising Vitamin A and, for example, an antioxidant such as Vitamin E, inserted into a first group of microspheres, and Vitamin C inserted into a second group of microspheres. A particularly preferred composition comprises a first group of microspheres containing Vitamin A at an average concentration of 0.014% and Vitamin E at an average concentration of 0.0005% by weight, and a second group of microspheres containing 0.02% by weight of Vitamin C.

Advantageously, in association to the groups of microspheres previously mentioned, such a composition may further contain, in addition to Vitamin A and Vitamin E, cosmetic compounds selected from the group comprising skin structurers, preferably squalan and sphingolipide complexes, skin micronutrients, preferably seaweed extract, sensorial agents, for example, moisteners such as glycerin and hydroxy prolisilan C, emollients such as buthylene glyclol and cethyl lactate and siliconas such as cyclomethicone, solar protection factors such as Parsol 1789 and Eusolex 6300, emulsifiers, preferably Carbopol 1342 associated to trietanolamin and soybean lecitin, thickeners, preferably xanthan gum; sequestrants, preferably EDTA, antioxidants such as BHT and dl-α-tocopherol, fragrances, conservants, water and mixtures thereof.

In one particular embodiment of the present invention, the composition containing Vitamin A and Vitamin C may be in the form of an emulsion and, in this case, the Vitamin C preferably used is L-ascorbic acid stabilized by hydrogen-bridge-forming compounds. Such processes of stabilizing L-ascorbic acid are described in applications PI 9704418-0 and PI 9704728-7, also filed by this same applicant.

As an illustrative example of another possible embodiment of the present invention, the composition is formulated as a gel in which the weight ratio of Vitamin C to Vitamin A is advantageously about 5:1, Vitamin C being present preferably in amounts of about 0.75% and Vitamin C being present in amounts of about 0.16 wt.%, based on the total weight of the composition. This gel composition may further contain thickeners such as carbopol, fragrances, conservants and water.

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: Fax 0055115549 2300
DANNEMANN, SIEMSEN, BIGLER
& IPANEMA MOREIRA
Rua Marqués de Olinda, 70
Botafogo
22251-040 - Rio de Janeiro - RJ
BRESIL

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	18.07.2000
Applicant's or agent's file reference: PE-3638	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/BR99/00072	03/09/1999	08/09/1998

International Patent Classification (IPC) or both national classification and IPC
A61K7/48

Applicant
INDUSTRIA E COMERCIO DE COSMETICOS NATURA LTDA.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 08/01/2001.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Grillenberger, S

Formalities officer (Incl. extension of time limits)
Götz, K
Telephone No. +49 89 2399 7381

WRITTEN OPINION

International application No. PCT/BR99/00072

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-8 as originally filed

Claims, No.:

1-16 as originally filed

Drawings, sheets:

1/1 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-4, 5-15, 16.

because:

☒ the said international application, or the said claims Nos. 1-4, 5-15, 16 relate to the following subject matter which does not require an international preliminary examination (*specify*):

WRITTEN OPINION International application No. PCT/BR99/00072

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-11, 15, 16
Inventive step (IS)	Claims	
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

WRITTEN OPINION
SEPARATE SHEET

International application No. PCT/BR99/00072

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-4 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 94 09756 A (UNILEVER PLC ;UNILEVER NV (NL)) 11 May 1994 (1994-05-11)
D2: FR-A-2 612 775 (THOREL JEAN) 30 September 1988 (1988-09-30)
D3: US-A-4 704 280 (BATES HARRY L) 3 November 1987 (1987-11-03)
D4: DATABASE WPI Section Ch, Week 198706 Derwent Publications Ltd., London, GB; Class B03, AN 1987-040730 XP002900871 & JP 62 000013 A (MIHAMA H), 6 January 1987 (1987-01-06)

For the assessment of the present claims 1-16 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

WRITTEN OPINION
SEPARATE SHEET

International application No. PCT/BR99/00072

Claim 1

1. Novelty: Art.33(1 and 2)

Document D1 destroys novelty for Claim 1, as there is claimed the "use" of a relevant composition (see reasoning for Claim 5 below) "in the repair of photo-damaged skin and/or in the prevention of damage to the skin due to exposure to ultraviolet light" (D1: claim 7, p.32, l.33, and p.17, l.25ff.), which implies "enhancing the cellular activity of an individual" as claimed in the Invention.

Claim 5

1. Novelty: Art.33(1 and 2)

A composition according to the Invention is not novel in the light of the state of the art. Again D1 discloses a composition comprising retinol or a derivative thereof (Vit A) (p.4, l.24-25) which "reduces skin blotchiness" and has "rejuvenating influence (...) on skin" (p.4, l.27-31), and Vit A behaves synergistically with a "skin lightening agent" (p.4, l.26), such as L-ascorbic acid and derivatives thereof (Vit C) (p.5, l.33). Example 3 (D1, p.23) provides the ingredients of such a composition, comprising 1%w/w of retinyl palmitate and 2%w/w of L-ascorbic acid (p.23, l.8-9), resulting in a weight ratio of Vit C/Vit A of 2:1 that falls within the range detailed in the Invention.

Moreover, Documents D2 and D3 describe similar compostions for comparable applications (D2 "prévention et traitement de la dégénérance cutanée", p.1, l.1-2; D3 "preparation for especially rough and dry skin", c.1, l.10-11) which comprise ascorbic acid at relevant levels (D2, cl.3: 0,1-2%w/w; D3: 0,12-6%w/w). Although the respective Vit A levels of the used fruit and vegetable extracts (D2: cl.1, and examples p.4-7) and an active Vit A-content expressed in USP-units (D3: c.1, l.66) may not be readily compared with %w/w-levels, the resulting Vit C/Vit A-ratios most probably cover the ranges as put forward in the Invention, and may also be novelty-destroying.

Claim 16

1. Novelty: Art.33(1 and 2)

Novelty of the subject-matter of Claim 16 is destroyed by several disclosures from the state of the art: D1 describes synergistic action of Vit C in compositions comprising Vit A (see above). D2 speaks about effects on the keratinization etc. of a combination of Vit C with Vit A, which go beyond the well-know effects of Vit C (D2, p.3, l.19-23).

D3 notices also special effects of the presented composition (see above) "when applied to skin which has been roughened over time..." (D3, c.1, .50-53). And D4 (l.11-14) explictly states that "it is found that when Vit A (...) is used with Vit C, a great amount of profibrinolysin activator is discharged from endothel cells of blood vessels due to a synergistic effect between both vitamins".

The combination of the features of dependent claims 12-14 is neither known from, nor rendered obvious by, the available prior art. It is suggested therefore that a new independent claim be drafted to include these features, bearing in mind that the features known in combination in claims 5-11 should be placed in the preamble of such claims in accordance with Rule 6.3(b) PCT.

Dependent claims 2-4, 6-11, and 15 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, the reasons being as follows:
Regarding Claims 2, 3, 6 and 8, the claimed Vit C/Vit A-ranges are anticipated by D1 (see above), as well as the addition of further antioxidant substances for the stabilization of the active ingredients, as described in Claims 4 and 15 (D1, p.17, l.14). The fact that the concept of the Invention is valid also for low concentrations of the active ingredients Vit C in association with Vit A as stated in Claims 7 and 9-11 of the Invention has already been described in D2 and D3 (see Vit C-ranges: D2, claim 3, p.8; D3, c.1, l.65. See also reasoning for Claim 5).

Re Item VIII
Certain observations on the International application

1. Interpretation of claims: Guidelines C-III.4.5.a
The meaning of "about" in claims referring to ingredient ranges is not clear, as it prevents the Invention from being unambiguously distinguished from the teaching in the prior art.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

-3 MAR PCT

To:
DANNEMANN, SIEMSEN, BIGLER
& IPANEMA MOREIRA
Attn. DANNEMANN, SIEMSEN
Rua Marqués de Olinda, 70
Botafogo
22251-040 - Rio de Janeiro - RJ
BRAZIL

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing *(day/month/year)* 25/04/2000	
Applicant's or agent's file reference PE-3638	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/BR 99/00072	International filing date *(day/month/year)* 03/09/1999

Applicant

INDUSTRIA E COMERCIO DE COSMETICOS NATURA LTDA.

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Claudia Aragone

Form PCT/ISA/220 (July 1998)

Gustavo

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PE-3638		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/BR 99/00072	03/09/1999	08/09/1998

Applicant

INDUSTRIA E COMERCIO DE COSMETICOS NATURA LTDA.

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1, 2

[X] as suggested by the applicant.

[ ] None of the figures.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/BR 99/00072

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-4, 16 all in part
because they relate to subject matter not required to be searched by this Authority, namely:
See next sheet

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Claims 1-4, 16 all in part relate to methods of treatment of the human or animal body by surgery or by therapy. See PCT, Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds compositions.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/BR 99/00072

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/48 A61K7/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 5 891 470 A (RINALDI MARIE A ET AL) 6 April 1999 (1999-04-06) column 7, line 45 -column 8, line 28 column 9, line 10 - line 30 column 10, line 16 -column 11, line 19; claims ---	1-16
P,X	WO 99 33439 A (ROBERTS RICHARD L ;GREENE JAMES A (US); SHAKLEE CORP (US); SIDDIQU) 8 July 1999 (1999-07-08) page 6, line 3 - line 14; claims 1-10,1624 ---	1-16
P,X	WO 99 24011 A (MURAD HOWARD) 20 May 1999 (1999-05-20) page 9, line 3 - line 15 page 10, line 17 - line 28; claims --- -/--	1-16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 February 2000	25.04.00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gerd Strandell/Eö

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/BR 99/00072

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	EP 0 229 561 A (MOET HENNESSY RECH) 22 July 1987 (1987-07-22) page 2, line 43 - line 46 page 3, line 38 - line 43 page 11, line 18 - line 31 page 13, line 1 - line 26; claims 1-3,11-14 ---	1-16
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/BR 99/00072

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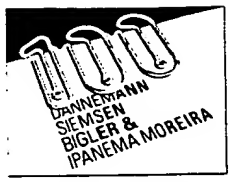

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3638 I

PROPRIEDADE INDUSTRIAL

PCT Chapter II

(by fax and courier)

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EUROPEAN PATENT OFFICE
INTERNATIONAL PRELIMINARY
EXAMINING AUTHORITY
D-80298 München
DE-Alemanha

Att. Mr. S. Grillenberger
Authorized officer/Examiner

São Paulo, October 18, 2000

Ref.: **PCT** – International Patent Application PCT/BR99/00072
Filed on September 03, 1999
INDÚSTRIA E COMÉRCIO DE COSMÉTICOS NATURA LTDA.
Reply to first written opinion
Our ref.: PE3638 (maj)

Dear Sirs:

In reply to the first written opinion mailed on July 18, 2000, applicant files herewith new pages 5 to 7 of the specification and claims, as follows:

Claims: Original claims 1-16 have been removed and a new set of claims (claims 1-6) are now presented which applicant believes recite patentable subject matter in view of the cited art.

Specification: a paragraph was inserted in the beginning of page 5 which highlights the advantage of introducing Vitamins C, A and E in microspheres.

Very truly yours,

Henrique Steuer I. de Mello
(Agent for the applicant)

The introduction of Vitamins C, A and E in microspheres increases their action and makes it possible for them to reach the deeper layers of the skin with greater, or even total, integrity, without degeneration of the product in the path between the application area and the place of action.

In a particularly preferred way, the cosmetic compositions according to the present invention are formulated in such a manner, that their components are contained in organic vectors such as microspheres and, more particularly, in microspheres or microcapsules containing biologically active material ("Talasferas") such as those defined in US Pat 5,395,620, or in Brazilian patent application PI 9706994-7, filed in the name of this same applicant.

The composition as described above may contain a plurality of said microspheres, in a dispersed form, comprising Vitamin A and, for example, an antioxidant such as Vitamin E, inserted into a first group of microspheres, and Vitamin C inserted into a second group of microspheres. A particularly preferred composition comprises a first group of microspheres containing Vitamin A at an average concentration of 0.014% and Vitamin E at an average concentration of 0.0005% by weight, and a second group of microspheres containing 0.02% by weight of Vitamin C.

Advantageously, in association to the groups of microspheres previously mentioned, such a composition may further contain, in addition to Vitamin A and Vitamin E, cosmetic compounds selected from the group comprising skin structurers, preferably squalan and sphingolipide complexes, skin micronutrients, preferably seaweed extract, sensorial agents, for example, moisteners such as glycerin and hydroxy prolisilan C, emollients such as buthylene glyclol and cethyl lactate and silicones such as cyclomethicone, solar protection factors such as Parsol 1789 and Eusolex 6300, emulsifiers, preferably Carbopol 1342 associated to trietanolamin and soybean lecitin, thickeners, preferably xanthan gum; sequestrants, preferably EDTA, antioxidants such as BHT and dl-α-tocopherol, fragrances, conservants, water and mixtures thereof.

In one particular embodiment of the present invention, the composition containing Vitamin A and Vitamin C may be in the form of an emulsion and, in this case, the Vitamin C preferably used is L-ascorbic acid stabilized by hydrogen-bridge-forming compounds. Such processes of stabilizing L-ascorbic acid are described in applications PI 9704418-0 and PI 9704728-7, also filed by this same applicant.

As an illustrative example of another possible embodiment of the present invention, the composition is formulated as a gel in which the weight ratio of Vitamin C to Vitamin A is advantageously about 5:1, Vitamin C being present preferably in amounts of about 0.75% and Vitamin C being present in amounts of about 0.16 wt.%, based on the total weight of the composition. This gel composition may further contain thickeners such as carbopol, fragrances, conservants and water.

Claims

1. Composition for enhancing the action of Vitamin A on the cellular activity of an individual, characterized in that it contains a plurality of dispersed microspheres, said plurality of microspheres comprising Vitamin A and an antioxidant preferably Vitamin E, inserted into a first group of microspheres, and Vitamin C inserted into a second group of microspheres.

2. Composition according to claim 1, characterized in that Vitamin C is present at a composition of about 0,02% by weight, and Vitamin A is present at a concentration of about 0,009% to 0,02% by weight, based on the total weight composition.

3. Composition according to claim 2, characterized in that Vitamin C is contained in the second group of microspheres at a concentration of 0,02%.

4. A composition according to claim 3, characterized in that it contains a first group of microspheres containing Vitamin A at an average concentration of about 0,014% by weight, based on the total weight of the composition.

5. A composition according to claim 4, characterized in that it contains a first group of microspheres containing Vitamin A at an average concentration of 0,014% and Vitamin E at an average concentration of 0,0005% by weight, and cosmetic compounds selected from the group consisting of skin structures, preferably squalan and sphingolipide complexes, micronutrients of the skin , preferably seaweed extract, sensorial agents, preferably moisteners such as glycerin and hydroxy prolisilan C, emollients such as buthylene glycol and cethyl lactate and silicones such as cyclometicone, solar protection factors such as Parsol 1789 and Eusolex 6300, emulsifiers, preferably Carbopol 1342 associated to trietanolamin any soybean lecitin thickeners, preferably xanthan gum; sequestrants, preferably EDTA, antioxidants such as BHT and dl-α-tocopherol, fragrances, conservants, water and mixtures thereof.

6. A composition according to claim 1 comprising Vitamin C in association with Vitamin A at a weight ration ranging from about 1:1 to about 10:1 of Vitamin C to Vitamin A.

In a particularly preferred way, the cosmetic compositions according to the present invention are formulated in such a manner, that their components are contained in organic vectors such as microspheres and, more particularly, in microspheres or microcapsules containing biologically active material ("Talasferas") such as those defined in US Pat 5,395,620, or in Brazilian patent application PI 9706994-7, filed in the name of this same applicant.

The composition as described above may contain a plurality of said microspheres, in a dispersed form, comprising Vitamin A and, for example, an antioxidant such as Vitamin E, inserted into a first group of microspheres, and Vitamin C inserted into a second group of microspheres. A particularly preferred composition comprises a first group of microspheres containing Vitamin A at an average concentration of 0.014% and Vitamin E at an average concentration of 0.0005% by weight, and a second group of microspheres containing 0.02% by weight of Vitamin C.

Advantageously, in association to the groups of microspheres previously mentioned, such a composition may further contain, in addition to Vitamin A and Vitamin E, cosmetic compounds selected from the group comprising skin structurers, preferably squalan and sphingolipide complexes, skin micronutrients, preferably seaweed extract, sensorial agents, for example, moisteners such as glycerin and hydroxy prolisilan C, emollients such as buthylene glyclol and cethyl lactate and silicones such as cyclomethicone, solar protection factors such as Parsol 1789 and Eusolex 6300, emulsifiers, preferably Carbopol 1342 associated to trietanolamin and soybean lecitin, thickeners, preferably xanthan gum; sequestrants, preferably EDTA, antioxidants such as BHT and dl-α-tocopherol, fragrances, conservants, water and mixtures thereof.

In one particular embodiment of the present invention, the composition containing Vitamin A and Vitamin C may be in the form of an emulsion and, in this case, the Vitamin C preferably used is L-ascorbic acid stabilized by hydrogen-bridge-forming compounds. Such processes of stabilizing L-ascorbic acid are described in applications PI 9704418-0 and PI 9704728-7, also filed by this same applicant.

As an illustrative example of another possible embodiment of the present invention, the composition is formulated as a gel in which the weight ratio of Vitamin C to Vitamin A is advantageously about 5:1, Vitamin C being present preferably in amounts of about 0.75% and Vitamin C being present in amounts of about 0.16 wt.%, based on the total

weight of the composition. This gel composition may further contain thickeners such as carbopol, fragrances, conservants and water.

Claims

1. A process for enhancing the action of Vitamin A on the cellular activity of an individual, characterized by comprising the association of Vitamin C to Vitamin A, which will be applied to said individual at a weight ratio ranging from about 1:1 to about 10:1 of Vitamin C to Vitamin A.

2. A process according to claim 1, characterized in that the weight ratio of Vitamin C to Vitamin A ranges from about 1:1 to about 5:1.

3. A process according to claim 2, characterized in that the weight ratio of Vitamin C to Vitamin A ranges from about 1:1 to about 2:1.

4. A process according to any one of claims 1 - 3, characterized in that Vitamin C is L-ascorbic acid stabilized with hydrogen-bridge-forming compounds.

5. A composition for enhancing the action of Vitamin A on the cellular activity of an individual, characterized by comprising Vitamin C in association with Vitamin A at a weight ratio ranging from about 1:1 to about 10:1 of Vitamin C to Vitamin A.

6. A composition according to claim 5, characterized in that the weight ratio of Vitamin C to Vitamin A ranges from about 1:1 to about 5:1.

7. A composition according to claim 6, characterized in that the weight ratio of Vitamin C to Vitamin A is of about 5:1, Vitamin C being present at a concentration of about 0.75% and Vitamin A being present at contents of about 0.16%, and in that it optionally contains thickeners, preferably carbopol, fragrances, conservants and water.

8. A composition according to claim 6, characterized in that the weight ratio of Vitamin C to Vitamin A ranges from about 1:1 to about 2:1.

9. A composition according to claim 5, characterized in that Vitamin C is present at a concentration of about 0.01% to 0.99% by weight, and Vitamin A is present at a concentration of about 0.008% to 0.20% by weight, based on the total weight of the composition.

10. A composition according to claim 8, characterized in that Vitamin C is present at a concentration of about 0.02% to 0.8% by weight, and Vitamin A is present at a concentration of about 0.009% to 0.16% by weight, based on the total weight of the composition.

11. A composition according to claim 5, characterized ion that Vitamin C is present at a composition of about 0.02% by weight, and Vitamin A is present at a concentration of about 0.009% to 0.02% by weight, based on the total weight of the composition.

12. A composition according to claim 11, characterized ion that it contains a plurality of dispersed microspheres, said plurality of microspheres comprising Vitamin A and an antioxidant, preferably Vitamin E, inserted into a first group of microspheres, and Vitamin C inserted into a second group of microspheres.

13. A composition according to claim 12, characterized in that Vitamin C is contained in the second group of microspheres at a concentration of 0.02%.

14. A composition according to claim 13, characterized ion that it contains a first group of microspheres containing Vitamin A at an average concentration of 0.014% and Vitamin E at an average concentration of 0.0005%, by weight, and cosmetic compounds selected from the group consisting of skin structurers, preferably squalan and sphingolipide complexes, micronutrients of the skin, preferably seaweed extract, sensorial agents, preferably moisteners such as glycerin and hydroxy prolisilan C, emollients such as buthylene glyclol and cethyl lactate and silicones such as cyclomethicone, solar protection factors such as Parsol 1789 and Eusolex 6300, emulsifiers, preferably Carbopol 1342 associated to trietanolamin and soybean lecitin, thickeners, preferably xanthan gum; sequestrants, preferably EDTA, antioxidants such as BHT and dl-α-tocopherol, fragances, conservants, water and mixtures thereof.

15. A composition according to any one of claims 5 - 14, characterized in that Vitamin C is L-ascorbic acid stabilized with hydrogen-bridge-forming compounds.

16. Use of Vitamin C, characterized in that it is for enhancing the action of Vitamin A on the cellular activity of an individual.

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(30) Priority Data:
PI 9803936-9 8 September 1998 (08.09.98) BR

(71) Applicant *(for all designated States except US)*: INDÚSTRIA E COMÉRCIO DE COSMÉTICOS NATURA LTDA. [BR/BR]; Rodovia Regis Bittencourt SN – Km 293, CEP-06850 Itapecerica da Serra, SP (BR).

(72) Inventors; and

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(81) Designated States: CA, JP, MX, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

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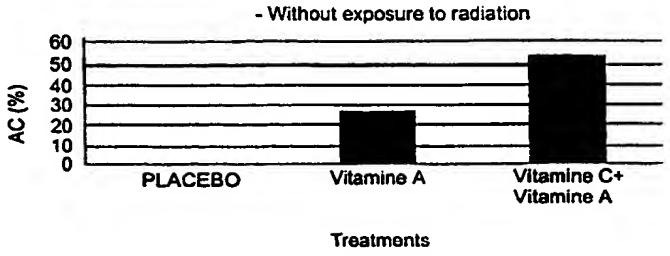
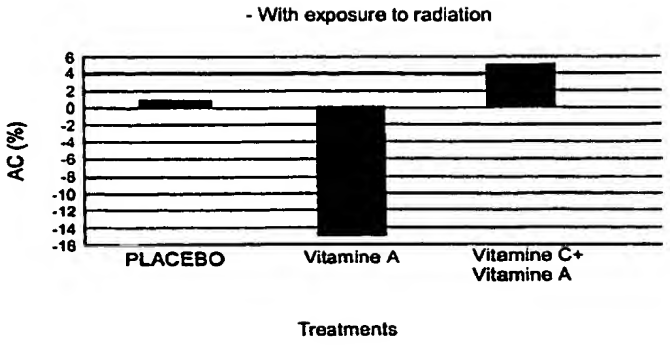
(54) Title: PROCESS AND COMPOSITION FOR ENHANCING THE ACTION OF VITAMIN A ON THE CELLULAR ACTIVITY OF AN INDIVIDUAL, AND USE OF VITAMIN C

(57) Abstract

The present invention refers to a process, a composition and the use of Vitamin C for enhancing the action of Vitamin A on the cellular activity of an individual. According to the invention, the association of Vitamin C to Vitamin A will be applied to said individual at a weight ratio ranging from 1:1 to about 10:1.





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INTERNATIONAL SEARCH REPORT

International Application No
PCT/BR 99/00072

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/48 A61K7/40

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P,X	US 5 891 470 A (RINALDI MARIE A ET AL) 6 April 1999 (1999-04-06) column 7, line 45 -column 8, line 28 column 9, line 10 - line 30 column 10, line 16 -column 11, line 19; claims ---	1-16
P,X	WO 99 33439 A (ROBERTS RICHARD L ;GREENE JAMES A (US); SHAKLEE CORP (US); SIDDIQU) 8 July 1999 (1999-07-08) page 6, line 3 - line 14; claims 1-10,1624 ---	1-16
P,X	WO 99 24011 A (MURAD HOWARD) 20 May 1999 (1999-05-20) page 9, line 3 - line 15 page 10, line 17 - line 28; claims --- -/--	1-16

[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/BR 99/00072

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 781 551 A (ADVANCED POLYMER SYSTEMS INC) 2 July 1997 (1997-07-02) page 2, line 43 -page 3, line 24 page 5, line 1 -page 6, line 21; claims ---	1-16
X	EP 0 229 561 A (MOET HENNESSY RECH) 22 July 1987 (1987-07-22) page 2, line 43 - line 46 page 3, line 38 - line 43 page 11, line 18 - line 31 page 13, line 1 - line 26; claims 1-3,11-14 ---	1-16
X	DATABASE STN INTERNATIONAL "Waging war on wrinkles" retrieved from FILE PROMT, accession no. 1998:413143 XP002900870 abstract & EUROPEAN COSMETIC MARKETS, August 1998 (1998-08), ISSN: 0957-1515 ---	1-16
X	WO 94 09756 A (UNILEVER PLC ;UNILEVER NV (NL)) 11 May 1994 (1994-05-11) page 4, line 24 - line 35 page 23, line 1 - line 25; claims ---	1-16
X	FR 2 612 775 A (THOREL JEAN) 30 September 1988 (1988-09-30) page 3, line 19 - line 23; claims 1-3 ---	1-16
X	US 4 704 280 A (BATES HARRY L) 3 November 1987 (1987-11-03) the whole document ---	1-16
X	DATABASE WPI Section Ch, Week 198706 Derwent Publications Ltd., London, GB; Class B03, AN 1987-040730 XP002900871 & JP 62 000013 A (MIHAMA H), 6 January 1987 (1987-01-06) abstract ---	5-11
X	WO 93 00015 A (KALAMAZOO HOLDINGS INC) 7 January 1993 (1993-01-07) claims 8,9 -----	5-11

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/BR 99/ 00072

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-4, 16 all in part
because they relate to subject matter not required to be searched by this Authority, namely:
See next sheet

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/BR 99/00072

Claims 1-4, 16 all in part relate to methods of treatment of the human or animal body by surgery or by therapy. See PCT, Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds compositions.

INTERNATIONAL SEARCH REPORT

[redacted]on on patent family members

[redacted]nal Application No
PCT/BR 99/00072

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5891470 A	06-04-1999	WO 9953904 A	28-10-1999
WO 9933439 A	08-07-1999	US 6015548 A	18-01-2000
		AU 1944599 A	19-07-1999
WO 9924011 A	20-05-1999	AU 1307299 A	31-05-1999
EP 0781551 A	02-07-1997	US 5851538 A	22-12-1998
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		CA 1298195 A	31-03-1992
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		JP 8502742 T	26-03-1996
		ZA 9308173 A	02-05-1995
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WO 9300015 A	07-01-1993	US 5230836 A	27-07-1993
		CA 2071415 A	21-12-1992
		EP 0590029 A	06-04-1994
		JP 6508748 T	06-10-1994
		US 5314686 A	24-05-1994
		US 5290481 A	01-03-1994
		US 5296249 A	22-03-1994

PATENT COOPERATION TREA

PCT

US

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PE-3638		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/BR 99/ 00072	03/09/1999	08/09/1998
Applicant		
INDUSTRIA E COMERCIO DE COSMETICOS NATURA LTDA.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1, 2

[X] as suggested by the applicant.

[ ] None of the figures.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/BR 99/00072

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-4, 16 all in part
because they relate to subject matter not required to be searched by this Authority, namely:
See next sheet

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

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Claims 1-4, 16 all in part relate to methods of treatment of the human or animal body by surgery or by therapy. See PCT, Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds compositions.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/BR 99/00072

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/48 A61K7/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 5 891 470 A (RINALDI MARIE A ET AL) 6 April 1999 (1999-04-06) column 7, line 45 -column 8, line 28 column 9, line 10 - line 30 column 10, line 16 -column 11, line 19; claims ---	1-16
P,X	WO 99 33439 A (ROBERTS RICHARD L ;GREENE JAMES A (US); SHAKLEE CORP (US); SIDDIQU) 8 July 1999 (1999-07-08) page 6, line 3 - line 14; claims 1-10,1624 ---	1-16
P,X	WO 99 24011 A (MURAD HOWARD) 20 May 1999 (1999-05-20) page 9, line 3 - line 15 page 10, line 17 - line 28; claims --- -/--	1-16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 February 2000	25.04.00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gerd Strandell/Eö

Form PCT/ISA/210 (second sheet) (July 1992)

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/BR 99/00072

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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